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Danazol Relieves Refractory Pruritus Associated With Myeloproliferative Disorders and Other Diseases

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Severe pruritus is frequently associated with myeloproliferative and other systemic illnesses, and often fails to respond to conventional measures. We used danazol (Danocrine™), a synthetic attenuated androgen, in the treatment of severe pruritus refractory to conventional therapy. Eight patients had myeloproliferative disorders (MPD), seven had autoimmune disorders, and seven had skin diseases. Danazol at 400–800 mg/day was administered, and previous medications were tapered off. When itching was controlled with danazol alone, the dosage was reduced or discontinued, and resumed if itching recurred. Clinical responses were graded, and side effects were monitored. Overall, in 12 of 22 patients refractory to other measures, itching was controlled with danazol alone. In 10 patients itching returned when danazol was discontinued or dosage was reduced, and was relieved upon resumption or increase of dosage. Danazol therapy was continued for up to 5 years in responders. No serious side effects were observed. Our experience indicates that danazol is a good alternative for patients with severe pruritus associated with myeloproliferative and other systemic disorders. © 1996 Wiley-Liss, Inc.

Key words: danazol, pruritus, myeloproliferative disorder, polycythemia vera

INTRODUCTION

Severe pruritus is frequently associated with myeloproliferative disorders (MPD) and other systemic illnesses such as immunologic, dermatologic, and neoplastic disorders [1–3]. Its severity ranges from mild and self-limiting to intensic chronic discomfort, occasionally so severe as to lead to suicidal ideation. Numerous treatments have been used in its management, including antihistamines, epinephrine, cimetidine, tricyclic antidepressants, β adrenergic blockers, and glucocorticoids [1–3]. In patients with MPD, phlebotomy and myelosupressive agents are often used in conjunction with antipruritc agents. However, many get little relief from these measures [4,5], and for these refractory cases there are few alternatives. We report here on the application of danazol (Danocrine™), a synthetic attenuated androgen, in patients with MPD and other systemic disorders who suffer severe itching [6].

MATERIALS AND METHODS

Patient Population

Twenty-two patients, 17 women and five men suffering from pruritus for at least 4 months, who had failed to respond to conventional measures such as antihistamines or glucocorticoids, were classified as "chronic refractory pruritus" and were recruited for the study consecutively from clinics. These included eight patients with MPD, seven with autoimmune disorders, and seven with skin diseases. See Table I for further data on the patient population. The median age was 59 years (66 for males, 57 for females). The study group was restricted to those who had failed on a series of conventional therapies.

Grading of Pruritus

Intensity was graded by functional handicap and the patient's own assessment, adapted from the classification used by Jackson et al. [7]:

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TABLE I. Summary of Patient Data and Classifications*

Patient	Age/sex	Diagnosis	Intensity of pruritus	Previous medications	Dose of danazol	Response to danazol	Time to respond	Retreatment[a]
Myeloproliferative diseases								
1	76/F	Polycythemia vera	4	AH, ALK, BZD, GC, HX	600–400	Excellent	1 week	A, B
2	73/F	Myelofibrosis	2	AH, ALK	400	Good	3 mo	B
3	68/M	Polycythemia vera	4	AH, GC	400–600	Excellent	1 week	NA
4	77/F	Myelofibrosis	3	AH, ALK, BZD, HD, HX	600	Good	2 weeks	A
5	71/M	Polycythemia vera	4	AH, GC, ALK, HD	600	Good	10 days	A
6	82/F	Polycythemia vera	2	AH, ALK	600	NR[b]		
7	68/F	Myelofibrosis	2	AH, GC	400	NR		
8	78/M	Myelofibrosis	3	AH, GC	600	NR		
Autoimmune diseases								
9	38/F	Systemic lupus eryth.	4	AH, GC, VC	400	Excellent	10 days	A, B
10	79/F	ITP	3	GC, AH	400	Excellent	1 day	A, B
11	51/F	Primary biliary cirrhosis	4	AH, GC, CL, CO, PLM	800–200	Excellent	1 day	A, B
12	38/F	Primary biliary cirrhosis	3	CL, PD, AH, CO	800–400	NR		
13	34/F	Systemic lupus eryth.	2	GC, AH	600	NR		
14	65/F	Systemic lupus eryth.	3	AH, GC	800	NR		
15	34/F	Systemic lupus eryth.	2	GC, AH	400	NR		
Skin diseases								
16	42/F	Urticaria	4	AH, BZD, EP, GC, ID, HX	600	Excellent	3 days	A, B
17	72/F	Urticaria	3	AH, GC	400	Excellent	1 day	A
18	72/F	Urticaria	2	AH, GC	600–200	Good	1 mo	NA
19	55/F	Lichen planus	2	AH, GC, GF	400	Good	3 mo	A, B
20	24/F	Erythema multiforme	2	AH, GC, HX	600	NR		
21	59/M	Idiopathic pruritus	2	AH, GC, BZD	600	NR		
22	56/M	Urticaria	3	AH, GC	800–600	NR		

*AH, antihistamines; ALK, alkylating agents; BZD, benzodiazepines; CL, cholestyramine; CO, colchicine; DEF, deferoxamine; EP, epinephrine; GC, glucocorticoids; GF, griseofulvin; HD, hydroxyurea; HX, hydroxyzin; ID, indomethacin; PLM, plasmapheresis; VC, vinca-alkaloids.
[a]A, relapsed after discontinuing danazol; responded again after retreatment; B, relapsed when dosage was reduced; responded again with dosage increase; NA, retreatment data not available.
[b]NR, non-responder.

Grade 0: No itching.

Grade 1: Mild. Able to perform daily activities; sleep unaffected; occasional episodes scattered through the day.

Grade 2: Moderate. Significant interference with daily activities; sleep occasionally affected; episodes more frequent.

Grade 3: Intermittently severe. Often incapacitated for daily activities; sleep difficult or impossible; episodes sporadic, intermittent.

Grade 4: Continuously severe. Completely incapacitated for daily activities; unable to sleep; continuous discomfort.

Danazol Treatments and Clinical Responses

At the outset, previous medications for itching were continued, and danazol 400–800 mg/day was added. As clinical improvement became apparent, previous medications for pruritus were tapered off and stopped. The efficacy of danazol alone for control of itching and duration of response was assessed in each patient. Clinical responses are classified as follows:

Excellent: Able to stop all other medications; itching controlled with danazol alone for ≥4 months.

Good: Itching relieved by danazol alone for ≥4 months, but occasionally required short-term use of previous drugs in smaller dosages.

No response: No improvement of any nature observed.

Patients with Excellent or Good responses were classified as "responders" to danazol, as opposed to nonresponders (NR).

Retreatments

When responses were sustained, a trial of reducing dosage or discontinuing danazol completely was attempted. When relapse occurred, danazol was resumed or dosage was increased. Retreatments were classified as follows:

Type A response: Patient relapsed after discontinuing danazol, but responded again after retreatment.

Type B response: When danazol dosage was reduced, pruritus relapsed, but again subsided with increase in dosage.

To avoid long-term side effects and to assess the need for long-term therapy, danazol was discontinued after ≥1

year of treatment, and duration of remissions and relapse patterns were evaluated. Danazol was resumed when relapse became evident, as described above.

Side Effects

All patients were followed closely to assess side effects and subjective/objective responses to danazol. Liver function tests were closely monitored, and any adverse effects were recorded. Any patient experiencing serious side effects was withdrawn from the study.

RESULTS

Clinical data on the patients are summarized in Table I.

Myeloproliferative Disorders (MPD)

This group included four patients with polycythemia vera (PV), and four with myelofibrosis. Their diseases were all under control and stable, without sign of acceleration; all had had the disease for >2 years. All had suffered from pruritus for ≥4 months with intensity scores of 2–4, and had failed to respond to the conventional measures indicated in Table I. In five of the eight, danazol relieved severe itching without need of their previous medications. In three of these responders, withdrawal of danazol was associated with relapse of pruritus, but resumption of therapy again relieved the symptoms; in one case pruritus relapsed after decreasing the dosage and was relieved by an increase in the dosage of danazol. A representative case study is given at the end of Results.

Autoimmune Disorders

Four patients with systemic lupus erythematosus (SLE), two with primary biliary cirrhosis, and one with chronic idiopathic thrombocytopenic purpura (ITP) constituted this group. In three of the four with SLE, pruritus was associated with papular or patch erythematous lesions. All suffered from grade 2–4 pruritus for ≥4 months and had failed to respond to conventional measures. Three of this group (one SLE with diffuse erythematous eruptions, one ITP, one primary biliary cirrhosis) responded to danazol with relief of pruritus. Examples follow.

Case 9. A 38-year-old woman had a long history of SLE with extensive diffuse erythematous skin eruptions involving mainly face, neck, and upper extremities. Her skin lesions and itching completely cleared on danazol therapy; withdrawal of danazol resulted in reappearance of skin lesions and itching in a few months, but eventually resolved with readministration of danazol. Several attempts to stop danazol resulted in recurrence of erythema and pruritus.

Case 11. A 51-year-old housewife with severe pruritus associated with primary biliary cirrhosis had failed on many other measures, including plasmapheresis. The effect of danazol in relieving her itching was immediate, with some relief reported on the second day of danazol. Cessation of danazol resulted in recurrence of itching within 1 week. Her itching has been under control by low-dose danazol for approximately 3 years now.

Dermatologic Disorders

Four of the seven with skin disorders (four chronic urticaria, one lichen planus, one erythema multiforme, and one idiopathic) were benefited by danazol. These included three of the four with chronic urticarias. An example follows.

Case 16. A 42-year-old dental hygienist had developed severe (grade 4) itching, leading to suicidal ideation for the previous 6 months. A range of conventional medications had been tried without success, after which she was tried on danazol. Her response was apparent within 3 days, when she reported a good night's sleep for the first time in 6 months. Itching returned with reduction of danazol, and was relieved again by restoring full dose. At the end of the second year danazol was discontinued, and she has remained free of itching for over 5 years at this writing.

Overall, 12 of 22 patients (54%) refractory to other measures responded to danazol therapy. The mean time to improvement was 22 days. In nine responders, withdrawal of danazol resulted in reappearance of pruritus, and retreatment with danazol again relieved itching (type A response). Data on retreatments is shown in Table I. In seven patients, reduction of dosage resulted in recurrence of pruritus, which was again relieved with increased dosage (type B response).

To avoid long-term side effects, after 1 year of danazol treatment we reduced or discontinued the drug. Four responders (one MPD, two chronic hives, and one SLE) were observed to promptly relapse following withdrawal of a short course of danazol therapy, but after at least 1 year of treatment remained in remission for extended periods after cessation of danazol.

Side Effects

Therapy was well-tolerated in most, but had to be discontinued in three patients: one with primary biliary cirrhosis due to worsening liver function tests (case 12 in Table I), a second with collagen vascular disease due to rash and elevation of liver function tests (case 15 in Table I), and a third with MPD owing to a skin rash (case 8 in Table I). All side effects reversed after discontinuation of danazol, and no other serious side effects were noted.

Representative Case Study (Case 1 of Table I)

A 76-year-old woman had been suffering from pruritus for 2.5 years. She had a history of PV (diagnosed 4 years previously) and had been treated with phlebotomies and alkylating agents with good control of the disease. However, her itching attacks had become more intense (grade

3–4) over the prior 6 months, and were particularly intense after bathing. She described these episodes as "a million ants biting all over me," reporting involuntary screams during the attacks, and alarming her neighbors at night; the agony drove her to thoughts of suicide. She had no other medical problems. She had consulted with many specialists, including a dermatologist and an allergist, and had been treated with numerous drugs (e.g., prednisone, benzodiazepines, antihistamines) without benefit. A skin biopsy was unremarkable. On examination there were many scratch wounds on the skin but it was free of rashes or ulcers. Blood counts showed hematocrit 46%; platelet count 744 per $10^3/\mu l$; leukocyte count 25.8 per $10^3/\mu l$; with 5% eosinophils, 2% basophils. She was placed back on allopurinol 300 mg/day and on busulfan 4 mg/day. Over the next month she continued to experience severe pruritus; therefore, danazol was introduced at 600 mg/day, then 800 mg/day. One week after beginning this medication, the patient expressed the first relief from her agony and was able to sleep at night. At 5 weeks on danazol, she dared to bathe and noted only a mild tolerable itching. When danazol was reduced to 200–400 mg/day, she noted recurrence of the pruritus. Danazol was then increased to 600 mg/day with improvement of itching; 3 months later it was again reduced to 400 mg/day. Danazol was discontinued after 2.5 years and she remained free of itching until 10 months later, when her complete blood count (CBC) was within normal limits. Resumption of danazol again controlled her pruritus. Over the last 5 years, many trials of reducing or stopping danazol were made in this patient but always resulted in relapses, necessitating readministration of danazol at 400 mg/day or higher to control pruritus. Itching occurred even when her platelet counts were below normal.

DISCUSSION

Danazol, a synthetic attenuated androgen, was initially formulated to treat endometriosis [8–10], and was subsequently found useful in treatment of hereditary angioedema [11], idiopathic thrombocytopenic purpura (ITP) [12,13], autoimmune hemolytic anemia (AIHA) [14], and other hematologic disorders [15]. Benefits of danazol were reported in chronic urticarias by Wong et al. [16]. Benefits of stanozolol another synthetic androgen, too, were reported in four patients with glucocorticoid-dependent urticaria [17].

Pruritus is a frequent symptom in MPD [1,3–5]. The pathophysiology underlying pruritus is quite complex. Mast cells and platelets release mediators upon stimulation that trigger inflammatory reactions to induce an itching sensation. Some of the known mediators of pruritus include histamine, kallikrein, bradykinin, neuropeptides, eicosanoids, platelet-activating factor (PAF), prostaglandin E_2 (PGE2), and serotonin [1–3]. Pruritus in MPD was believed to be due to the quantity of histamine released from mast cells [18]. However, tryptase levels measured in polycythemic patients experiencing pruritus failed to show significant increase after shower, as compared to before, demonstrating that mast cell degranulation cannot be solely responsible for the pruritus in those patients [19]. It was suggested that release of prostaglandins and serotonin from platelets plays a role in pruritus [5,7,19,20].

The mechanism(s) by which danazol arrests pruritus remains speculative. Danazol apparently controls itching of diverse origins, including autoimmunity, liver diseases, and neoplasms. This suggests that it acts on a common pathway of itching. Shape changes of red blood cells (RBC) in patients on danazol therapy were reported, and the RBC became resistant to osmotic lysis [21]. It has been directly demonstrated by high-pressure liquid chromatography (HPLC) assay that danazol preferentially accumulates in cell membranes [22]. We speculate that danazol intercalation in the lipid bilayer stabilizes cell membranes and reduces cell excitability, possibly inhibiting the release of PGE2, serotonin, and histamine from mast cells and platelets. The immune modulating action of danazol [23,24] may also play a role.

It might be argued that the relief of pruritus is due to spontaneous remission or placebo effects rather than to danazol. Placebo effects are unlikely because all patients studied had failed on at least two other therapies. It is also unlikely that spontaneous remission could account for the results, since all patients studied had persistent and refractory pruritus of long duration. Withdrawal of danazol or reduction of dose schedule repeatedly resulted in recurrence of pruritus; and readministration or increase in dosage again relieved severe itching in most responders. These observations strongly argue against placebo effects. Nonetheless, a larger-scale, controlled prospective study is called for to verify the results reported here.

Management of refractory pruritus associated with MPD and other systemic disorders presents a serious challenge to the clinician [25]. Danazol offers a viable safe option for many patients suffering from this painful syndrome.

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